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A Case of Possible Atypical Demyelinating Event of the Central Nervous System Following COVID-19

Abstract

After the novel coronavirus disease outbreak first began in Wuhan, China in December 2019, the viral epidemic has quickly spread across the world and it is now a major public health concern. Here we present a 21-year-old male with encephalomyelitis following intermittent vomiting and malaise for 4 days. He reported upper respiratory signs and symptoms 2 weeks before this presentation. Two cerebrospinal fluid (CSF) analyses were notable for mononuclear pleocytosis, elevated protein (more than 100 mg/dl), and hypoglycorrhachia. Brain MRI showed

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bilateral posterior internal capsule lesions extending to the ventral portion of the pons and a marbled splenium hyperintensity pattern. Cervical and thoracic MRI showed longitudinally extensive transverse myelitis (LETM); none of which were enhanced with gadolinium. Both the AQP4 and MOG antibodies were negative. Spiral chest computed tomography (CT) scan conformed to COVID-19 as did the high IgG level against coronavirus, but the oropharyngeal swabs were negative. Neurological manifestations of COVID-19 have not been adequately studied. Some COVID-19 patients, especially those suffering from a serious disease, are highly likely to have central nervous system (CNS) involvement. Our case is a post-COVID-19 demyelinating event in the CNS.

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Key words: COVID-19, Demyelinating event, ADEM, NMOSD

1. Introduction

Coronavirus neuro-invasive characteristics have been identified in humans. It has been shown that severe infection with SARS-CoV-2 is associated with neurological manifestations such as headache, epilepsy, cerebrovascular events and encephalitis (Bohmwald, Galvez et al. 2018, Asadi-Pooya and Simani 2020). Coronavirus probably enters the CNS through the olfactory bulb, which could cause inflammation and subsequent axonal damage or demyelination (Desforges, Le Coupanec et al. 2020). We present a young man with COVID-19 and acute encephalomyelitis with newly diagnosed possible demyelinating lesions in the CNS.

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2. Case Report

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A previously healthy 21-year-old male with a Bachelor of Science was referred to the emergency room of our hospital on March 20th, 2020. His family reported that he had a fever with chills, non-productive cough and a sore throat 2 weeks before admission, but no hyposmia or hypogeusia. All symptoms decreased in severity within 10 days, after which he developed significant loss of appetite, recurrent vomiting with food intolerance and generalized malaise. Following 3 days of repeated vomiting, he experienced weakness and paresthesia of the lower limbs, which continued throughout the day. On the next day, family members found that he had urinary retention, increased paraparesis severity and weakness of the upper limbs; he also became drowsy. The patient had no headache, vertigo, diplopia, dysphagia, neck pain or blurred vision.

On examination, his blood pressure was 110/85 mmHg and his pulse was 98 beats per minute. His temperature was 37.9°C, his respiratory rate 20 per minute and his oxygen saturation 94% while he was breathing ambient air. The patient was lethargic but obeyed simple verbal commands. There was no evidence of nuchal rigidity, Kernig's or Brudzinski's signs. His pupils were equally reactive to light. The muscular strength was 4+/5 in the upper limbs and 2/5 in the lower limbs. He had normal deep tendon reflexes in all four limbs and Babinski's sign was absent. The position and light touch sensation were impaired in both lower limbs; additionally, he had a T8 sensory level. The abdominal cutaneous reflex was absent in all directions. A spiral chest CT scan revealed left lung peripheral ground-glass opacities (Figure 1A). The patient was transferred to the specialized intensive care unit designated for patients with SARS-CoV-2, and a nasopharyngeal swab was obtained for detection of COVID-19 genome by real-time polymerase chain reaction. Initial laboratory tests as well as erythrocyte sedimentation rate and c-reactive protein were normal. Screening tests for human immunodeficiency virus type 1 (HIV-1) and type

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2 (HIV-2) antibodies and also tests for hepatitis B virus (HBV) antigen and antibodies and hepatitis C virus (HCV) antibody were negative. With clinical suspicion of acute disseminated encephalomyelitis (ADEM) along with suspected COVID-19, 250 milliliter plasma exchange was started daily for 5 days. MRI of cervical and thoracic spine revealed LETM with an intramedullary lesion extending > 3 segments in the spinal cord. Sagittal T2-weighted fluid-attenuated inversion recovery (FLAIR) brain MRI showed bilateral long corticospinal tract lesions in internal capsules extending to the cerebral peduncles and pons. Moreover, there was a heterogenous, marbled pattern hyperintensity in the splenium of the corpus callosum (Figure 2B, C, D and E) without diffusion-weighted restrictions nor contrast enhancements. The spinal tap showed cloudy and pale-yellow CSF. In the analysis, there were 150 total nucleated cells per microliter, of which 60% were lymphocytes. The CSF protein level was 281 mg/dL and the glucose level was 34 mg/dL, with a serum glucose level of 110 mg/dL concomitantly. No organism was detected in Gram's staining. Empirical treatment with intravenous vancomycin, meropenem and acyclovir was initiated. A PCR panel of CSF for all viruses including Herpes Simplex 1 and 2 (HSV1 and HSV2), Hemophilus influenza, etc. and all bacterial/fungal agents including Mycobacterium tuberculosis complex, Listeria monocytogenes, etc. were negative. Serological testing for the antinuclear antibody, antiphospholipid antibodies, human leukocyte antigen (HLA) B5, B51, and Angiotensin-converting enzyme (ACE) were unremarkable. The CSF and serum autoimmune panel investigations such as Anti-N-methyl-d-aspartate (NMDA) receptor were negative as were blood cultures for organisms. Two COVID-19 nasopharyngeal swab tests were negative, as was the CSF assay for the genome of the virus. An electroencephalogram revealed a normal background rhythm (8 Hz), with no epileptiform discharges. On day 4, the patient became afebrile and his mental status improved. Aquaporin-4 receptor (AQP4), and myelin oligodendrocyte glycoprotein (MOG)

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antibodies in the serum and CSF were assessed, which were both negative and Oligoclonal band (OCB) in CSF was unobtainable. The findings of the second CSF analysis, 72 hours after the first tap, showed 250 total nucleated cells per microliter, with 60% lymphocytes. The CSF protein level was 111 mg/dL and the glucose level was 65 mg/dL. Serologic tests for COVID-19 were requested, which revealed a negative result for IgM, but the IgG level was 1.6 (positive >1.1). At the end of the second week, the upper limb weakness improved, but the force of the lower limbs was 3+/5.

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3. Discussion

The main clinical manifestation of human coronaviruses is respiratory involvement and the main cause of death is an acute respiratory failure. However, there have been reports of extra respiratory manifestations such as neurological findings (Ashrafi, Azizimalamiri et al.). Recent studies suggest possible mechanisms leading to COVID-19 neuro-invasive and neurotropic characteristics. The first is a direct viral injury to the CNS via blood circulation or nasal epithelium (Wu, Xu et al. 2020). Although there are some suggestive case reports of encephalitis (Wu, Xu et al. 2020, Ye, Ren et al. 2020), there is no definite proof that the SARS-CoV-2 virus affects the CNS directly. The second cause of nervous tissue damage results from the unpredictable effects of the host immune response after an acute infection. Guillain-Barré syndrome (GBS), as peripheral demyelination, is an example of this mechanism. Some cases of COVID-19-related GBS have been reported (Toscano, Palmerini et al. 2020), but the evidence of causality or effect is weak (Toscano, Palmerini et al. 2020, Zhao, Shen et al. 2020). The third mechanism is an indirect injury of the CNS due to systemic disease, particularly in patients who are critically ill. The last mechanism is overactivation of the immune response, which results in cytokine release (Yin, Wang et al. 2004). According to the literature, neurotropic coronaviruses could induce a "cytokine storm" by releasing a large number of inflammatory markers (Bohmwald, Galvez et al.

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2018), which could activate molecular changes and also reactivate immune-mediated processes (Kim, Heo et al. 2017). Together, these mechanisms could induce delayed nervous system damage and neurological complications (Klein, Garber et al. 2017).

Studies on SARS-CoV-1 revealed a delayed self-reactive T-cell suppression due to viral replication, which leads to neuroinflammation, demyelination or axonal damage of the CNS (Savarin and Bergmann 2017, Cheng, Skinner et al. 2019). Moreover, experimental models of coronavirus-induced neurological disease have shown that sustained CNS inflammation of infected animals correlates with increased demyelination (Savarin and Bergmann 2017). Recent studies have shown that the novel coronavirus appears to be able to cross the blood-brain barrier and cause acute or delayed CNS demyelination or axonal damage (Desforges, Le Coupanec et al. 2020). A case of acute necrotizing encephalomyelitis following COVID-19 is reported as an acute CNS injury (Poyiadji, Shahin et al. 2020). Moreover, a recent report revealed CNS delayed demyelinating events following COVID-19 (Zanin, Saraceno et al. 2020). According to our patient's examination, imaging and laboratory findings, there are two differential diagnoses, including ADEM or neuromyelitis optica spectrum disorder (NMOSD). In the absence of histopathological evidence, we could not settle on an exact diagnosis for the patient. The presenting symptoms including new-onset fever and drowsiness along with neurological deficit after regressing respiratory illness suggested a postviral ADEM; however, in the absence of lesions' enhancement as well as callosal involvement, ADEM is less likely. On the other hand, the history of sudden onset of recurrent vomiting, which could indicate postrema syndrome, along with LETM, and corticospinal tract and corpus callosum hyperintensities are more indicative of NMOSD (Wingerchuk, Banwell et al. 2015). Encephalopathy, however, as a presenting symptom, is uncommon in NMOSD. In the present study, COVID-19 was not detected in CSF or the

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nasopharynx presumably due to delayed immune-mediated CNS damage that occurred after the virus was cleared. Moreover, this could be explained by the low sensitivity of the system or delayed sampling (Panciani, Saraceno et al. 2020, Ye, Ren et al. 2020, Zanin, Saraceno et al. 2020).

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4. Conclusion

Severe COVID-19 may affect the CNS and have various acute or delayed neurological complications. During the COVID-19 pandemic, it is important to consider SARS-CoV-2 infection when seeing patients with neurological manifestations, especially those needing immune-modulator therapy, since the established recommendations are insufficient at this time.

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Acknowledgments: This study received no funds.

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